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Twelfth day of January 2004

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PROVISIONAL SPECIFICATION FOR THE INVENTION ENTITLED:

A Method of Treating a Stiffened Vessel

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This invention is best described in the following statement:

A METHOD OF TREATING A STIFFENED VESSEL

Technical Field

The present invention relates to the treatment of a stiffened vessel, such as a blood vessel, and in particular relates to, but is not limited to, a method of treating a stiffened and dilatated aorta to reduce cardiac load.

Background of the Invention

The left ventricle of the heart pumps cyclically to deliver oxygenated blood to the body via the aorta. The cyclic pumping of the left ventricle of the heart includes a systole stage and a diastole stage, depicted in Figures 1 and 2 respectively.

During the systole stage, the left ventricle 1 contracts, pumping blood to the aorta 2 through the aortic valve 3. Contraction of the left ventricle 1 increases the pressure in the aorta 2, causing the aorta 2 to expand, as depicted in Figure 1. At various points 4 along the aorta, the aorta wall may be subject to peripheral resistance restricting the ability of the aorta to expand. The systolic blood pressure is the maximum blood pressure in the aorta during the systole stage.

During the diastole stage, the left ventricle 1 relaxes and the aortic valve 3 closes to stop a back flow of blood into the left ventricle 1. The left atrium 5 contracts to fill the left ventricle 1 with further blood in preparation for the next systole stage. During the diastole stage, the blood pressure within the aorta 2 reduces to what is termed the diastolic blood pressure. The reduced pressure at this stage causes the wall of the aorta 2 to relax (contract), restoring it back to its original diameter. The blood is accordingly pumped through the aorta and into the arteries in a pulsating manner.

The ability of the aorta 2 to expand and restore during the systole and diastole stages is dependent upon the elasticity of the aorta wall which results from the elastin fibres of the aorta wall.

Systolic blood pressure progressively increases with ageing that begins in childhood until the eighth or ninth decade, whereas diastolic blood pressure tends to remain constant after the fifth or sixth decade. Consequently, the pulse pressure, being the pressure differential between the systolic and diastolic blood pressure, increases beyond the age of 50. This form of hypertension is termed isolated systolic hypertension and increases in frequency with increasing age.

Various studies have shown that elevated systolic pressure is associated with a greater risk of heart failure, stroke, and acute myocardial dysfunction, and that treatment

of elevated systolic pressure can delay or prevent such adverse events even when diastolic pressure is normal or low.

A number of studies have also shown that, in patients over 50, there is a stronger association between adverse cardiovascular (particularly coronary) events and pulse pressure than systolic or diastolic pressure in isolation. Accordingly, for any given systolic pressure, the diastolic pressure is inversely related to the risk of adverse cardiovascular events, possibly due to reduction in coronary perfusion with decreased diastolic pressure.

Heart failure is reported to effect 2 to 5 percent of people in Western societies aged over 65, and 10 percent of those aged over 75. It is also reported to be the leading cause of hospital admission and readmission in Americans older than 65.

The increase in systolic blood pressure with age is largely a result of stiffening of the aorta and large elastic arteries. Dilatation of the aorta/arteries is associated with this stiffening. The stiffening and dilatation is a result of the repetitive cyclic stress applied to the aorta wall during expansion and subsequent relaxation of the aorta. The cyclic stresses applied to the aorta wall result in fatigue fracture and fragmentation of the elastin fibres which provide the aorta wall with its elasticity. The mechanical properties of the aorta wall gradually become dominated by inelastic collagen. The breakdown of the elastin fibres results in the aorta becoming inelastic and stiff, thereby losing its capability to restore to its original diameter after expansion during the systole stage. The aorta accordingly remains permanently dilatated. This dilatation may result in an increase in diameter of the aorta from approximately 20 mm up to as large as 30 mm or more.

Aortic stiffening alters the left ventricular systolic pressure in two ways. First, there is a greater rise in pressure at the time of peak aortic flow in the systole stage as a result of failure of the aorta to expand as blood is pumped from the left ventricle. Secondly, failure of the aorta to expand increases the blood pulse wave velocity in the aorta. This causes pressure waves reflected from peripheral sites to return to the aorta earlier than usual, boosting pressure in the late systole stage. This early return of the reflected wave to the ascending aorta during the ventricular ejection of systole is detrimental since systolic pressure and left ventricular afterload is increased. The early return of the reflected wave also reduces diastolic pressure and the capacity for myocardial perfusion. Each of these factors results in an increase in cardiac load of the left ventricle.

The most effective means of treating, or preventing, heart failure is to reduce cardiac load either pharmacologically or mechanically. Mechanical reduction of cardiac load using intra-aortic balloon counter pulsation and ventricular assist devices have proven effective. However, intra-aortic balloon counter pulsation can only be used as a temporary treatment. Ventricular assist devices are also expensive and temporary measures.

Object of the Invention

It is an object of the present invention to overcome or substantially ameliorate at least one of the above disadvantages.

Summary of the Invention

In a first aspect the present invention provides a method of treating a stiffened and dilatated blood vessel, the method comprising at least substantially encasing a portion of said vessel with an elastic membrane such that said membrane engages said vessel to thereby reduce the diameter of said vessel.

Preferably the blood vessel is an artery.

More preferably the blood vessel is the aorta.

The membrane may be in the form of a sheet, said vessel portion being encased by wrapping said membrane sheet around the circumferential periphery of said vessel portion and securing opposing end portions of said membrane.

The membrane sheet may be wrapped around either the entire circumferential periphery of said vessel portion, or only about a majority of the circumferential periphery.

The opposing ends of said membrane sheet may be secured by suturing or by way of clamp means.

The membrane sheet may be formed by slitting a cylindrical membrane.

The membrane may be in the form of a spiral, said vessel portion being encased by spirally wrapping said membrane spiral around the circumferential periphery of said vessel portion.

Typically, said membrane has a stiffness approximating that of a healthy non-stiffened blood vessel.

Preferably said membrane is formed of an elastic silicon polymer material.

Preferably, said method is carried out thoracoscopically.

In a second aspect the present invention provides a method of reducing the left ventricular load in a subject, the method comprising at least substantially encasing a

portion of a stiffened and dilatated blood vessel in the subject with an elastic membrane such that said membrane engages said vessel to thereby reduce the diameter of said vessel.

In a third aspect the present invention provides a method of treating or preventing cardiac failure in a subject in need of such treatment or prevention, the method comprising at least substantially encasing a portion of a stiffened and dilatated blood vessel in said subject with an elastic membrane such that said membrane engages said vessel to thereby reduce the diameter of said vessel.

In a fourth aspect the present invention provides a method of increasing the effective elasticity of a vessel in a biological system, the method comprising at least substantially encasing a portion of said vessel with an elastic membrane such that said membrane engages said vessel to thereby reduce the diameter of said vessel.

Brief Description of the Drawings

Preferred forms of the present invention will now be described by way of example with reference to the accompanying drawings, wherein:

Figure 1 is a schematic partial cross-sectional view of a heart and aorta in systole.

Figure 2 is a schematic partial cross-sectional view of the heart and aorta of Figure 1 in diastole.

Figure 3 is a perspective view of a portion of an aorta encased by a membrane.

Figure 4 is a schematic cross-sectional view of the aorta portion of Figure 3.

Figure 5 is a perspective view of a portion of an aorta encased by another membrane.

Figure 6 is a perspective view of a portion of an aorta encased by a spiral membrane.

Figure 7 is a front elevation view of an aorta having an anastomosed graft encased by an elastic membrane.

Detailed Description of the Preferred Embodiments

Referring specifically to Figures 3 and 4, a stiffened and dilatated aorta 2 is treated by at least substantially encasing a portion of the aorta 2 with an elastic membrane 6. The elastic membrane 6 engages the wall of the aorta 2, contracting the dilatated aorta to reduce its diameter back towards that of the healthy aorta in the diastole stage (as per that depicted in Figure 2). The membrane 6 will accordingly contract the aorta 2 in the

diastole stage and all internal blood pressure loads during diastole acting on the aorta wall will be carried by the elastic membrane 6. As blood pressure increases during the systole stage, the increasing pressure acting on the membrane 6 will stretch the membrane 6, allowing the aorta 2 to expand back towards its dilatated state in the usual manner. If the elastic membrane 6 has a stiffness approximating that of a healthy non-stiffened aorta, the elastic membrane 6 will take substantially the entire load applied by the blood pressure during systole, as the aorta 2 will only start to take up any appreciable load once expanded beyond its now naturally permanently enlarged state.

With substantially the entire load placed on the aorta during the diastole and systole stages being carried by the elastic membrane 6, the effective stiffness of the encased portion of aorta 2 will be substantially equal to that of the elastic membrane 6. Accordingly, if the stiffness of the elastic membrane 6 approximates that of a healthy non-stiffened aorta, the aorta 2 will expand and restore in much the same manner as a healthy aorta.

Reducing the effective stiffness of the aorta 2 in this manner, providing for elastic expansion of the aorta 2 during the systole stage, will reduce ascending aortic and left ventricular pressure during systole. Similarly, with the encased aorta 2 being restored to its reduced diameter during diastole, the diastolic pressure will increase in the same general manner as for a healthy aorta.

Decreasing aortic and left ventricular pressure during systole will aid left ventricular ejection and reduce left ventricular load, especially in the presence of cardiac failure, and decrease myocardial oxygen demand. The increase in aortic diastolic pressure resulting from normal relaxation of the aorta during diastole will improve myocardial blood flow and oxygen supply. The reduction in pulse pressure resulting from a decrease of systolic pressure and increase in diastolic pressure will reduce pulsatile external work and thus increase the efficiency of blood circulation. An effective treatment to reduce cardiac load is thus provided using a simple, passive device.

The membrane 6 depicted in Figure 3 is in the form of a membrane sheet which encases the aorta portion 2 by wrapping the membrane sheet 6 around the circumferential periphery of the aorta and securing opposing end portions 7, 8 of the membrane sheet 6. The membrane end portions 7, 8 may be secured by a suture 9 as depicted, or alternatively a clamp or other means of securing the opposing end portions 7, 8 may be utilised.

Whilst the membrane sheet 6 depicted is wrapped around the entire circumferential periphery of the aorta portion 2, an effective result may still be achieved by encasing the aorta portion 2 with a membrane 6' wrapped only around a majority of the circumferential periphery of the aorta portion 2 in the manner depicted in Figure 5. So long as the elastic membrane 6' is wrapped around more than half of the circumferential periphery of the aorta portion 2, an effective reduction of the aorta diameter will be achieved and pressure loads acting on the aorta wall will be largely taken up by the elastic membrane 6'. It is preferred that the entire circumferential periphery of the aorta portion 2 be encased by the membrane, however lack of access around the entire periphery, may prevent full wrapping. Such lack of full peripheral access may particularly occur at sites where arteries branch from the aorta, such as from the descending aorta.

Referring to Figure 6, an alternative form of elastic membrane 6'' is depicted which is particularly suitable for use around a portion of the aorta 2 where multiple arteries 10 branch from the aorta 2. The elastic membrane 6'' is in the form of a spiral strip of material that is spirally wound around the circumferential periphery of the aorta portion 2 to encase the same. The spacing between successive coils of the spiral can be manipulated as required to provide for passage of the arteries 10 branching from the aorta portion 2. Having the spiral membrane 6'' only engage the periphery of the aorta portion 2 at discrete locations along its length will still be sufficient to reduce the diameter of the aorta portion and bear the majority of the load acting on the aorta wall to thereby increase the effective elasticity of the aorta portion 2.

A suitable class of materials for use in fabrication of the elastic membrane 6 is elastic silicon polymers. Such materials are immunologically inert, durable and readily sutured, clamped or secured in various other manners. A particularly suitable example of such a material is an elastic silicon polymer developed by Medtronic for use as a simulated ascending aorta for in-vitro testing of artificial aortic valves. The material is typically supplied in cylindrical lengths with a wall thickness of approximately 2 mm and can be slit down one side to form a suitable membrane sheet 6 as depicted in Figure 3. This material has mechanical properties similar to that of a healthy young human aorta. As the material is a silicon polymer, it has a linear stress-strain relationship in uniaxial tensile testing, unlike the natural aorta that has a sigmoid stress-strain relation in uniaxial tensile testing. Nevertheless, the dilatation of the cylindrical material during physiologic

blood flow approximates the dilatation of a healthy young aorta at normal physiologic blood flow and pressure.

The elastic membrane material has a 12% stiffness when pulsatile flow is pumped through the material in cylindrical form at physiological blood pressure. In the context of this specification, 12% stiffness refers to a 12% increase in diameter of the cylinder during systole at physiologic blood flow and pressure as compared to the diastolic diameter of the cylinder. A stiffer elastic membrane material with 4% stiffness has also been used effectively.

The elastic membrane sheets 6 may be fabricated and utilised in any of various lengths. If a significant length of aorta 2 requires treatment the entire effected aorta portion may be wrapped with a single elastic membrane 6 if accessibility to the aorta makes this feasible. It will, however, typically be more feasible, given the confines of the treatment site, to wrap successive short lengths of elastic membrane 6 around successive portions of the aorta 2. Membrane lengths of the order of 3 cm are expected to be manageable in most applications.

For patients undergoing coronary artery bypass grafting, segments of elastic membrane may be applied to the ascending aorta and proximal arch of the aorta through the median sternotomy wound created during the bypass procedure. Segments of elastic membrane can also be applied to the distal arch and ascending thoracic aorta through a left thoracotomy or left thoracoscopic technique leaving intercostal arteries intact.

The procedure may also be undertaken on patients undergoing other forms of cardiac surgery such as valve repair or replacement or replacement of the aortic root or ascending aorta. The procedure is also suitable for being carried out on patients undergoing thoracic surgery such as pneumonectomy, lobectomy or excision of carcinoma or any other surgical procedure where there is a risk of precipitating acute heart failure in a patient with impaired left ventricular function when aortic dilatation and stiffening are present.

When the procedure is carried out during surgery where median sternotomy is not performed, the ascending aorta and arch of the aorta can be accessed through right thoracotomy, right thoracoscopic procedure or minimal access upper hemi sternotomy.

As well as utilising the elastic membrane 6 to treat the aorta, the technique is also expected to be useful in treating similar stiffness and dilatation in the major arteries.

Whilst it is envisaged that the treatment will be suitable as a long term solution for many patients suffering cardiac failure or other problems associated with aortic

stiffening, the present treatment may also be utilised as a short term solution for patients awaiting the supply of a replacement heart for heart transplant surgery. The treatment is also expected to be suitable for a short term solution to improve the cardiovascular function and strength of patients requiring coronary bypass surgery but who are perceived to be too weak to be subjected to such surgery. For such patients, a three to six month period following aortic treatment with elastic membrane wrapping may be sufficient to prepare the patient for primary bypass surgery. Such treatments may be conducted through minimally invasive thoracoscopic techniques.

For these applications where the elastic membrane aortic treatment is conducted as a short term treatment, the elastic membrane may be formed of a biodegradable material that will degrade once its purpose has been fulfilled.

To assess the effective increase in the elasticity of the aorta by application of the elastic membrane wrap treatment described, trials were carried out on the aorta of five sheep. To stimulate a dilatated and stiffened portion of aorta, a 22 mm Dacron material aortic graft 11 was anastomosed in line with a resected portion of aorta 2 as depicted in Figure 7. With the dacron material of the graft 11 being stiff and of an increased diameter as compared to the native aorta material, the graft simulated a stiffened and dilatated aorta. The dacron graft was then wrapped with an elastic membrane 6 as described above. Both 18 and 20 mm diameter wrapped membranes 6 were utilised, to restrict the diameter of the dacron graft 11 to the same. Measurements of stiffness of the aorta were taken at a base line prior to resection, following anastomosis of the dacron graft 11, and subsequently with the elastic membrane wrap 6 in place. The stiffness measured was the pressure-strain elastic modulus (E_p):

$E_p = (dP/dD) \times D$

where D = diastolic aortic diameter;

dD = change in aortic diameter;

dP = change in aortic pressure.

The measurements were made both in normotension and in hypertension. The hypertension was induced by infusion of aramine.

As expected, anastomosis of the dacron graft resulted in an increase in elastic modulus. This increase was approximately 11 times that of the base line healthy aorta in normotension and 16 times in hypertension. Addition of the elastic membrane wrap reduced the elastic modulus of the aorta by a factor of approximately 4 in normotension

and 8 in hypertension to a value of approximately 2 times that of the base line healthy aorta in normotension and 3 times in hypertension.

Whilst the above method has been described in particular for use in treating a stiffened and dilatated aorta or other blood vessel, it is envisaged that the method will also be effective in increasing the effective elasticity of vessels in other biological systems including the urinary tract of the urinary system.

DATED this Nineteenth Day of December, 2002

Unisearch Limited

Patent Attorneys for the Applicant

SPRUSON & FERGUSON

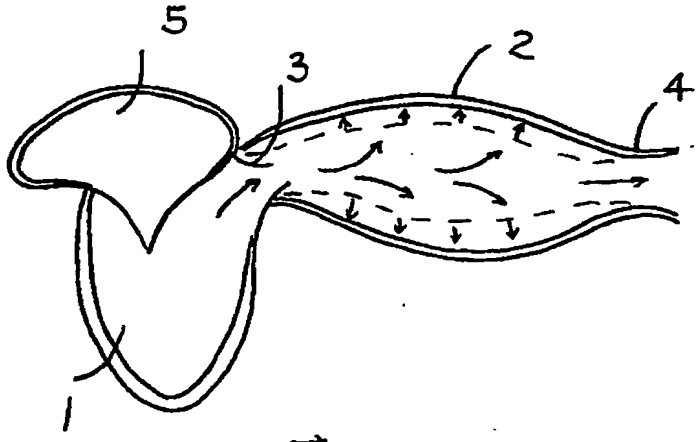

Fig. 1

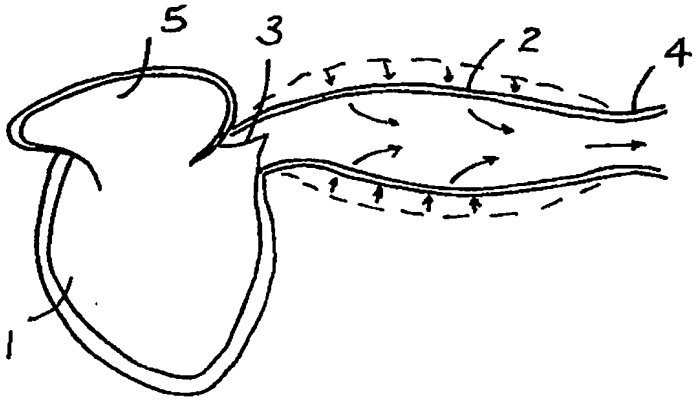

Fig. 2

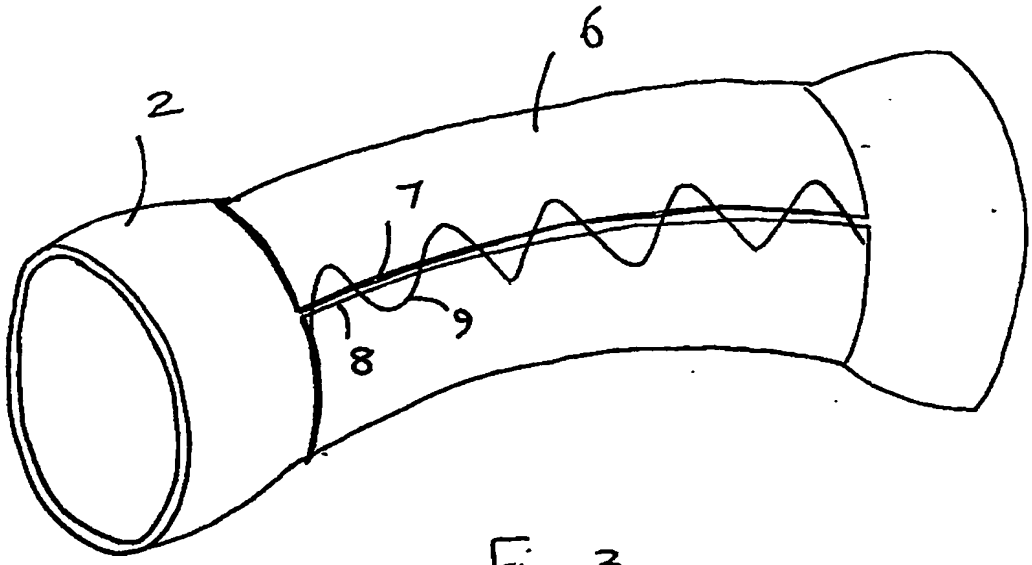

Fig. 3

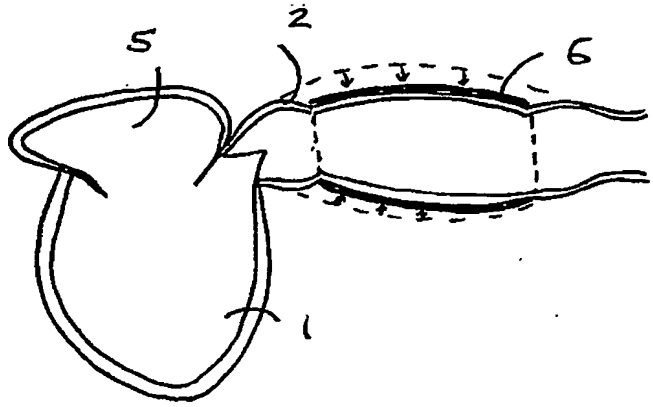

Fig. 4

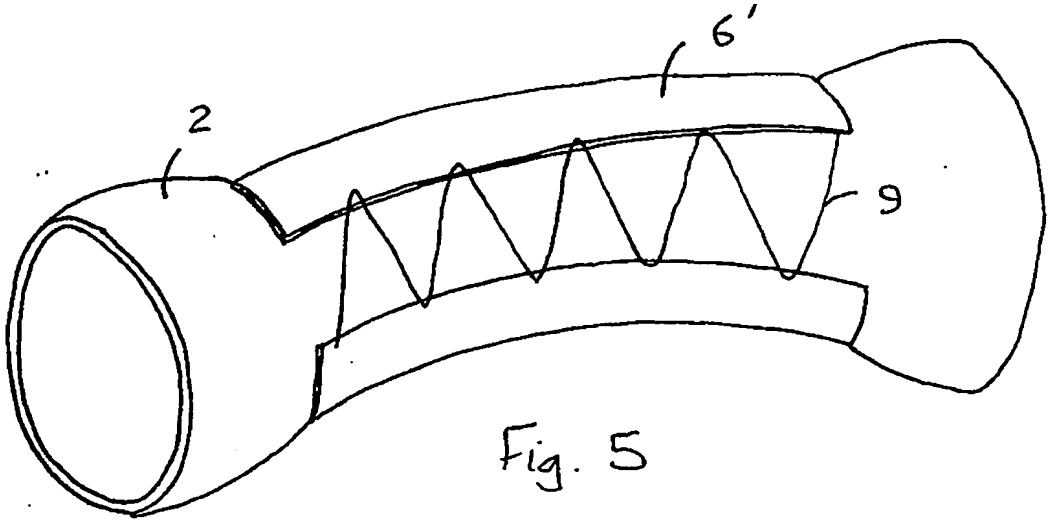

Fig. 5

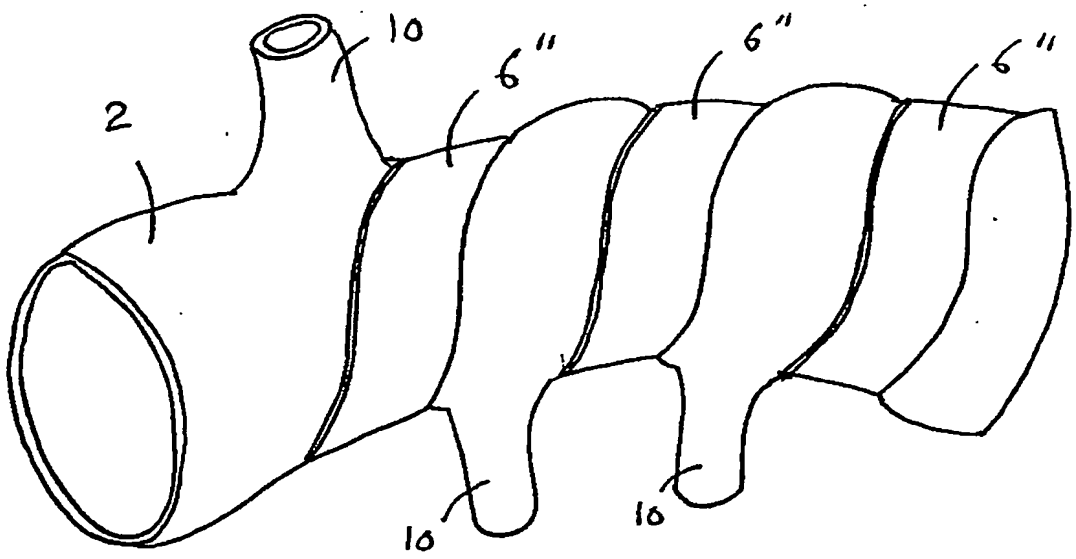

Fig. 6

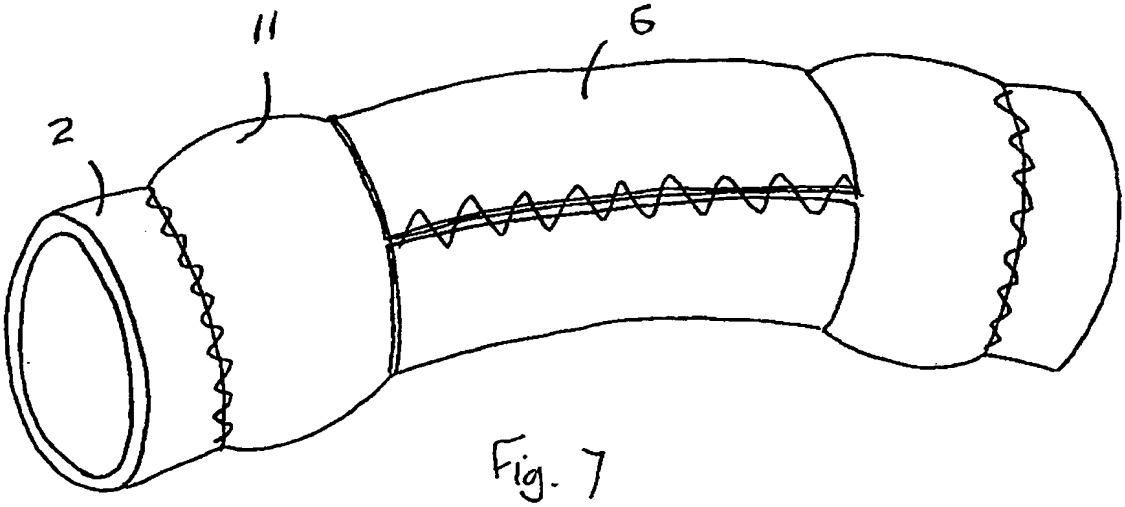

Fig. 7

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